

CYCLODEXTRIN COMPOSITIONS

5 The present invention relates to pharmaceutical compositions, in particular to compositions having broad spectrum anthelmintic activity, and their use in human and veterinary medicine.

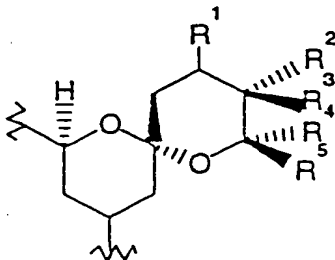
10 The use of cyclodextrins as complexing agents for active substances is known and has been previously described in, for example, US-A-4,727,064 to Pitha (amorphous drug/cyclodextrin complexes), EP-A-0 149 197 to Janssen (inclusion complexes of medicaments with a b-cyclodextrin ether or ester) and EP-A-0 392 608 to Procter & Gamble (solid consumer product compositions containing small particle size cyclodextrin complexes).

15 It has now been found that cyclodextrins are useful for stabilizing certain anthelmintic compounds.

20 The invention provides a pharmaceutical composition comprising at least one anthelmintically active compound which is an avermectin or milbemycin, in the form of a complex with at least one cyclodextrin. It is believed that the avermectins and milbemycins form inclusion complexes with the cyclodextrins and such inclusion complexes therefore form a particular aspect of the invention.

When used herein the term "pharmaceutical" includes the term "veterinary" and the term "pharmaceutically" includes the term "veterinarily".

Suitable avermectins and milbemycins for use in carrying out the present invention include commercially available compounds such as milbemycin, ivermectin, doramectin, moxidectin, nemadectin, and abamectin. Further suitable compounds are of partial formula (i)

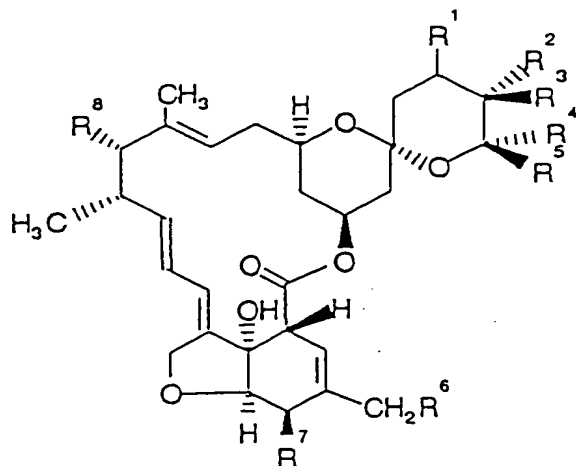


(i)

wherein  $R^1$  is an optionally substituted amino or imino group such as optionally O-substituted oxyimino, optionally N-substituted hydrazone or optionally N-substituted semicarbazone, and  $R^2$  to  $R^5$  are the same or different and each is hydrogen or an organic radical.

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Preferred compounds of formula (i) are compounds of formula (I):



(I)

wherein  $R^1$  to  $R^5$  are as defined above,  $R^6$  is hydrogen or optionally protected hydroxy;  $R^7$  is alkoxy, optionally protected hydroxy, oxo or optionally O-substituted oxyimino; and  $R^8$  is hydrogen, optionally protected hydroxy, or a group 4'-(a-L-oleandrosyl)-a-L-oleandrosyloxy or a-L-oleandrosyloxy wherein the terminal hydroxy group is optionally protected.

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Compounds of formula (I), and processes for their preparation, are described in EP-A-0 259 779, EP-A-0 293 549, EP-A-0 307 225, GB-A-2 192 630, EP-A-0 260 536, EP-A-0 260 537, EP-A-0 307 220, and EP-A-0 421 568.

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Preferably, the compound of formula (I) is a compound in accordance with EP-A-0 421 568 more especially a compound wherein  $R^1$  is O-substituted oxyimino,  $R^2$  to  $R^4$  are hydrogen,  $R^5$  is an organic radical,  $R^6$  and  $R^8$  are hydrogen, and  $R^7$  is hydroxy.

Suitable avermectins are those of EP-A-0677054, particularly 5-oximino-22,23-dihydro-25-cyclohexylavermectin B1 monosaccharide (Example 5).

Suitable protecting groups for hydroxy include TBDMS (t-butyldimethylsilyl), and acyl (alkanoyloxy). Further suitable protecting groups are described in, for example, "Protective Groups in Organic Synthesis" Theodora W. Greene, Wiley-Interscience 1981 Ch 2, 10-86.

When any of R<sup>2</sup> to R<sup>5</sup> is an organic radical it may advantageously be selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heterocyclyl, mono-, bi- and tri-cycloalkyl, mono-, bi- and tri-cycloalkenyl and aralkyl.

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As used herein alkyl includes straight and branched C<sub>1-20</sub>, more especially C<sub>1-12</sub>, particularly C<sub>1-6</sub> alkyl, and alkenyl and alkynyl include straight and branched C<sub>2-20</sub>, more especially C<sub>2-12</sub>, particularly C<sub>2-6</sub> alkenyl and alkynyl.

10 When any of R<sup>2</sup> to R<sup>5</sup> comprises an alkyl, alkenyl or alkynyl moiety that moiety may optionally be substituted by one or more substituents selected from the group consisting of hydroxy, alkoxy, alkylthio, oxo, halogen, trifluoromethyl, and optionally substituted amino.

15 When used herein the term 'aryl' includes phenyl and naphthyl optionally substituted with up to five, preferably up to three, groups selected from halogen, C<sub>1-6</sub> alkyl, aryl, C<sub>1-6</sub> alkoxy, halo substituted (C<sub>1-6</sub>) alkyl, hydroxy, amino, nitro, carboxy, C<sub>1-6</sub> alkoxycarbonyl, C<sub>1-6</sub> alkoxycarbonyl-(C<sub>1-6</sub>)-alkyl, C<sub>1-6</sub> alkylcarbonyloxy, or C<sub>1-6</sub> alkylcarbonyl groups.

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The term 'heterocyclyl' includes saturated, unsaturated and aromatic single or fused rings comprising up to four hetero atoms in the ring selected from oxygen, nitrogen and sulphur and optionally substituted with up to three halogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, halo-(C<sub>1-6</sub>)-alkyl, hydroxy, amino, carboxy, C<sub>1-6</sub> alkoxycarbonyl, C<sub>1-6</sub>

25 alkoxycarbonyl(C<sub>1-6</sub>) alkyl, aryl or oxo groups.

Suitably the heterocyclic ring comprises from 4 to 7 ring atoms, preferably 5 to 6 atoms.

30 The term 'halogen' refers to fluorine, chlorine, bromine and iodine.

Particularly suitable substituents for an amino or imino group such as an oxime, hydrazone or semicarbazone group include one or more organic radicals as defined hereinabove for R<sup>2</sup> to R<sup>5</sup>, for example the substituents set out in EP-A-0 288 205,

35 EP-A-0 259 779, EP-A-0 260 537, EP-A-0 260 536, GB-A-2 192 630, EP-A-0 307 225 and EP-A-0 421 568.

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Those skilled in the art will appreciate that an N-substituted imino group such as an oxime may exist as either an E or Z isomer, or as a mixture of E and Z isomers, and that an E or Z isomer may be converted to the other isomer or to a mixture of isomers by standard techniques such as acid treatment.

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As used herein mono-, bi- and tri-cycloalkyl include C<sub>3-20</sub>, especially C<sub>3-12</sub>, more especially C<sub>4-8</sub>, groups, and mono-, bi- and tri-cycloalkenyl include C<sub>4-20</sub>, especially C<sub>4-12</sub>, more especially C<sub>5-8</sub> groups. When any of R<sup>2</sup> to R<sup>5</sup> comprises a mono-, bi- or tri-cycloalkyl or mono-, bi- or tri-cycloalkenyl moiety, that moiety may be substituted as set out above for alkyl, alkenyl, and alkynyl, and/or by one or more substituents selected from the group consisting of methylene and alkyl. Bicyclic and tricyclic groups may be fused or bridged and are preferably attached via a carbon atom which is common to two rings.

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15 Any two of R<sup>2</sup> to R<sup>5</sup> may be taken together with the carbon atom(s) to which they are attached to designate a cycloalkyl, cycloalkenyl, aryl or heterocyclyl group which may optionally be substituted as set out above.

20 Cyclodextrins for use in carrying out the present invention include substituted and unsubstituted cyclodextrins containing from six to twelve glucose units, such as a-, b- and g-cyclodextrins, their derivatives, and mixtures thereof. Derivatives include C<sub>1-6</sub> alkyl and hydroxy C<sub>1-6</sub> alkyl ethers, such as methyl b-cyclodextrin, hydroxyethyl b-cyclodextrin, and hydroxypropyl b-cyclodextrin, as well as polymers and copolymers such as b-cyclodextrin/epichlorohydrin copolymers. Substituted  
25 cyclodextrins may exhibit differing degrees of substitution, and may be amorphous or crystalline. Unsubstituted cyclodextrins are usually crystalline.

Cyclodextrins are described in *inter alia* US-A-3,426,011, US-A-3,453,257, US-A-3,459,731, US-A-3,553,191, US-A-3,565,887, US-A-4,535,152, US-A-4,616,008,  
30 US-A-4,638,058, US-A-4,746,734, and US-A-4,678,598. Cyclodextrins and mixtures of cyclodextrins are commercially available from *inter alia* Amaizo, Hammond, Indiana, USA; Roquette Corporation, Gurnee, Illinois, USA; Chinoin Pharmaceutical and Chemical Works Ltd., Budapest, Hungary; Aldrich Chemical Company, Milwaukee, Wisconsin, USA; Wacker Chemie, Germany; and Ensui  
35 Sugar Refining Company, Yokohama, Japan.

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In one aspect, the cyclodextrin for use in the present invention is a crystalline cyclodextrin such as b-cyclodextrin or a pure substituted cyclodextrin such as dimethyl b-cyclodextrin, which is commercially available.

- 5 The pharmaceutical composition of the invention is of use in the treatment of helminthiasis of the human or non-human animal body, and particularly for treating nematode infestations of domestic and farm animals.

10 Accordingly, the present invention also provides a method of treating helminthiasis, particularly nematode infestations in domestic animals, which method comprises administering to the patient in need thereof an anthelmintically effective amount of a pharmaceutical composition of the invention.

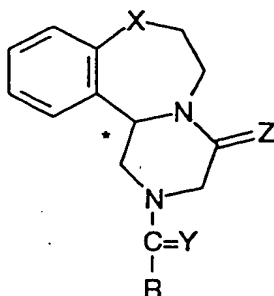
15 Accordingly the present invention also provides a pharmaceutical composition, as hereinbefore defined, (hereinafter called "the composition") for use in the treatment of the human or non-human animal body, especially for treating helminthiasis and particularly for treating nematode infestations of domestic animals, especially dogs and cats. Particular nematode infestations for treatment include trichuris, toxascaris and ancylostoma.

20 Suitably, the composition may comprise a shaped composition, such as a bolus, tablet or capsule, or can be mixed directly with animal foodstuffs. Optionally the composition contains one or more lubricants, dispersants, binders, fillers, colours, flavours, and the like. Preferably the composition is a tablet which has been  
25 rendered more palatable by the inclusion of a food extract such as desiccated liver or fish meal.

The composition may also be added to animal feed. It will be convenient to formulate these animal feed compositions with a multi-dose of the anthelmintic drug  
30 so that the animal takes in an appropriate quantity of the composition along with its diet. It will also be convenient to present the composition as a premix for addition to the feed.

35 The composition may optionally additionally comprise further active ingredients such as further anthelmintic compounds, more especially at least one compound with activity against tapeworm such as *Taenia taeniaeformis* and *Dipylidium caninum*. Such compounds include compounds of formula (II)

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(II)

- in which R is optionally substituted phenyl; C<sub>3-8</sub> cycloalkyl; C<sub>5-8</sub> cycloalkenyl; C<sub>1-8</sub> alkyl which may be straight or branched; C<sub>2-8</sub> alkenyl which may be straight or branched; 5- or 6- membered heterocyclyl; or optionally substituted phenyl C<sub>1-4</sub> alkyl, each of Y and Z, which may be the same or different, is oxygen or sulphur; and X is a bond, -CH<sub>2</sub>-, or oxygen.
- Compounds of formula (II) wherein X is -CH<sub>2</sub>- or oxygen, and processes for their production, are described in EP-A-0 134 984 and EP-A-0 187 012. An exemplary such compound is epsiprantel (2-(cyclohexylcarbonyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2]benzazepine).
- Compounds of formula (II) wherein X is a bond, and processes for their production, are described in DE-A-1 795 728, DE-A-24 41 261, DE-A-23 62 539 and by Andrews et al in Medicinal Research Reviews (John Wiley & Sons, Inc.) Vol.3, No. 2, 147-200 (1983). An exemplary such compound is praziquantel (2-cyclohexylcarbonyl[1,2,3,6,7,11b]hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one).
- Compounds of formula (II) have an asymmetric carbon atom marked by an asterisk in formula (II) and may therefore exist in at least two stereoisomeric forms. The present invention encompasses all isomers of the compounds of formula (II) whether pure or admixed with other isomers in any proportion.
- When R is optionally substituted phenyl, it may be substituted with one or more moieties selected from halogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, nitro, amino, mono-or-di-C<sub>1-6</sub> alkylamino, and hydroxy.
- When R is heterocyclyl, it may be a 5 or 6-membered saturated or unsaturated group containing up to three hetero-atoms selected from oxygen, sulphur and nitrogen. It will be appreciated that unsaturated heterocyclyl groups suitably include aromatic heterocyclyl groups.

The term "halogen" refers to fluorine, chlorine, bromine and iodine.

A preferred R group is cyclohexyl.

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Compounds of formula (I) have anthelmintic activity especially against tapeworm such as *Taenia taeniaeformis* and *Dipylidium caninum*.

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Suitably the composition comprises of sufficient material to provide a dose of from 0.001 to 100 mg of the avermectin or milbemycin compound(s) per kg of animal body weight per dose, more suitably 0.01 to 10mg/kg per dose. Suitably the ratio of avermectin/milbemycin(s) : cyclodextrin(s) is in the range 1 : 1 to 1 : 10 preferably about 1:4, w/w. The composition may further comprise sufficient material to provide a dose of from 0.01 to 250mg of a compound of formula (II) per kg of animal

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Compositions in accordance with the invention enable the stability of the avermectin/milbemycin compound to be improved, even in the presence of certain excipients, such as foodstuffs or food extracts, which could otherwise cause degradation of the avermectin/milbemycin.

20

In one aspect, the composition is formulated in such a way as to delay release of the active avermectin/milbemycin compound *in vivo*. Release of the active compound may be delayed by inclusion of a polymer, in particular a cellulose derivative such as ethyl cellulose or a synthetic polymer such as Eudragit, which is a mixed copolymer of methacrylic acid and methyl methacrylate and has a mean molecular weight of about 135,000. "Eudragit" is a Trade Mark of Röhm Pharma GmbH.

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A further aspect of the invention provides a process for the preparation of a composition in accordance with the invention, which process comprises preparing a mixture of at least one avermectin or milbemycin, at least one cyclodextrin, and, optionally, a solvent or mixture of solvents, and then removing the solvent or mixture of solvents if present, for example by freeze-drying, spray drying, filtration and/or evaporation. The complex thus formed is then optionally admixed with one or more excipients as defined above and/or shaped to form a bolus, tablet or capsule.

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Suitable solvent-free methods in accordance with the invention include grinding and kneading.

5 Suitable solvents include polar solvents such as methanol. The preparation of the mixture is suitably carried out for example at ambient temperature. Evaporation of solvent may be carried out under reduced pressure, for example at about 60°C.

The following Examples illustrate the invention.

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# Example 1

## Methyl b-cyclodextrin/milbemycin complex

- 5 Methyl-b-cyclodextrin (randomly methylated) and milbemycin (the compound of Example 6 of EP-A-0 421 568, mixture of E- and Z-isomers) were weighed out in the ratio 4:1. Each was dissolved in 20 ml of methanol and the two solutions combined in a 100 ml round bottomed flask. The methanol was then removed under reduced pressure at 60°C under constant rotation on a Buchi Rotavapor. The material
- 10 obtained was removed from the flask and transferred to a 100 ml beaker and left under vacuum for a further 30 mins at 60°C to remove any residual traces of methanol. The material was then ground in a pestle and mortar to obtain a fine powder.
- 15 Milbemycin complexed as described in Example 1 was compared with the uncomplexed milbemycin with respect to its rate of degradation. Shelf life predictions were obtained using the Arrhenius method. The results are reported below:

### 20 Uncomplexed milbemycin

Time (weeks)	50°C	25°C
8.0	43.7%	
12.0		96.2%

\* Shelf life prediction: 30 weeks (6-153) [>99.9% significance]

### 25 Complex of Example 1

Time (weeks)	50°C	25°C
8.0	95.0%	
12.0		100.8%

\* Shelf life prediction: not possible: no significant decomposition at 25°C.

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\* Shelf life equals period required for 10% potency loss at 25°C.

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**Example 2**

**$\beta$ -Cyclodextrin/milbemycin complex**

- 5 7g of milbemycin was weighed and transferred to a ceramic mortar to which 63g of  $\beta$ -cyclodextrin was weighed and added. The two powders were then mixed with a spatula until reasonably homogeneous and then ground with a pestle for at least 45 minutes. The product obtained is a complex of milbemycin and  $\beta$ -cyclodextrin.

10 **Example 3**

**$\beta$ -Cyclodextrin/milbemycin complex**

- 15 7g of milbemycin was weighed and transferred to a 1000 ml steel vessel to which 63g of  $\beta$ -cyclodextrin was weighed and added. To the vessel were added sufficient steel ball bearings to ensure efficient grinding. The vessel is then sealed and rotated at a constant velocity (*ca* 30 r.p.m.) for one hour. The vessel is then opened and the material removed. The product is a complex of milbemycin and  $\beta$ -cyclodextrin.

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#### Example 4

#### Palatable pet tablets

Ingredient	% (w/w)
<b>Pet Tab Granules</b>	
Complex of Example 2 or 3	1.40
Epsiprantel	7.69
Desiccated Liver	20.78
Fish Meal	15.59
Protex 111	0.52
Starch 1500	5.20
Lactose BP	16.47
Avicel PH102	15.59
Texapon L100	0.26
	(83.50)
<b>Compression Mix</b>	
Pet Tab Granules	83.50
Aerosil 200	0.50
Avicel PH102	15.00
Magnesium Stearate	1.00
	(100.00)

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#### Pet Tablet Granules

- 1) Weigh out all materials
- 10 2) Dissolve Texapon in deionised water to give a solution of 2.5% w/v.
- 3) Pass all other materials through 2mm sieve screen into a planetary mixer bowl.
- 15 4) Mix materials in planetary mixer until homogeneous.
- 5) Granulate material with Texapon solution and further deionised water until granulate of correct consistency is obtained.

- 6) Dry granules at 60°C until moisture content is below 5% (Karl-Fischer).
7. Weigh granules and calculate the amount of extra granular materials needed.

#### 5 Compression Mix

- 1) Weigh out pet tab granules and all extra granular materials.
- 2) Pass all extra granular materials through 500µm sieve.
- 10 3) Mix extra granular materials and pet tab granules in a planetary mixer until homogeneous.
- 15 4) Proceed to compression.

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**Example 5**

**Palatable Pet Tablets**

<b>Ingredient</b>	<b>% (w/w)</b>
<b>Pet Tab Granules</b>	
Epsiprantel	7.69
Desiccated Liver	20.78
Fish Meal	15.59
Protex 111	0.52
Starch 1500	5.20
Lactose BP	16.47
Avicel PH102	15.59
Texapon L100	0.26
	(82.10)
<b>Compression Mix</b>	
Pet Tab Granules	82.10
Complex of Example 2 or 3	1.40
Aerosil 200	0.50
Avicel PH102	15.00
Magnesium Stearate	1.00
	(100.00)

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Method: as for Example 4

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